American Red Cross

National Headquarters

June 30, 2000

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Re: Prescription Drug Marketing Act of 1987; Prescription Drug Amendments of 1992; Policies, Requirements, and Administrative Procedures; Delay of Effective Date; Reopening of Administrative Record [65 FR 25639; Docket Nos. 92N-0297 and 88N-0258 (May 3, 2000)]

Dear Drs. Woodcock and Zoon:

The American Red Cross (ARC or Red Cross) appreciates the action taken by the Food and Drug Administration (FDA) to delay implementation of certain provisions of the final rule concerning the Prescription Drug Marketing Act (PDMA), as modified by the Prescription Drug Amendments of 1992 and the FDA Modernization Act of 1997. Red Cross is submitting this letter to participate in the public comment process as provided by FDA.

With approximately 50% of the nation's blood supply being produced by the American Red Cross, we are the nation's single largest producer of blood products. Thus, Red Cross has a direct interest in the implementation of PDMA and its amendments.

Red Cross is concerned that the final rule does not exclude plasma derivatives from the procedures and requirements of PDMA. This concern is based on the final rule's language that, in effect, will not allow Red Cross to distribute such life-saving products as Immune Globulin Intravenous (IGIV) at a time when their availability has been tenuous. Further, the final rule may also discourage research and development on new technologies and safer products.

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To address this concern, Red Cross urges FDA to modify the regulation to exclude organizations that provide blood, blood components and plasma derivatives. In addition to the collection, processing, and distribution of blood products and components, blood banks are often responsible for the recovery of plasma from blood donors and/or plasma derivatives. Excluding blood banks from the final rule's definition of "health care entity" would allow for the continued distribution of blood products and plasma derivatives without disruption, and help ensure the most efficient distribution of these life-saving products in the future. Alternatively, we suggest that FDA expand the exclusion for blood or blood components to include plasma derivatives.

We have attached two documents to support this request:

Attachment 1 describes our current distribution system, and explains how this final rule's requirements will impact ARC's products and customers. Distribution and product data are included where appropriate, which will help demonstrate the potential disruption in providing these products to the patients who need them.

Attachment 2 contains our letter to you dated February 4, 2000 describing our views on the Congressional intent of the PDMA and recommendations for revisions to the final rule.

We appreciate this opportunity to express our views. If you have any questions, please feel free to contact me at 703-807-5351 or Anita Ducca, Director, Regulatory Affairs at 703-312-5601.

Sincerely,

Jacquelyn Fredrick
Senior Vice President
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cc: Joanne Binkley
Jay Epstein, M.D.
Steven F. Falter
Diane Maloney
Robert Yetter
Ann Wion, Esq.

Attachments

Comments by the American Red Cross On the Delay of Effective Date and Reopening of Administrative Record Final Rule Implementing the Prescription Drug Manufacturing Act (PDMA) Docket Nos. 92N-0297 and 88N-0258 [65 FR 25639 (May 3, 2000)]

I. Introduction

The American Red Cross (ARC/Red Cross) is an independent non-profit corporation and the largest provider of blood products and services in the United States. Each year, the Red Cross collects, processes, and distributes nearly half the nation's blood supply, including donations of approximately 6 million units of whole blood. Blood collection for transfusion is conducted throughout the nation by 36 regional Red Cross blood centers. The American Red Cross processes units of whole blood into specific components such as red blood cells, platelets, and other products that are distributed to thousands of hospitals and other health care providers in the United States.

Approximately 1,000,000 liters of plasma recovered from Red Cross volunteer blood donors are annually processed or fractionated into plasma derivatives. These plasma derivatives are distributed under the American Red Cross label to hospitals, hemophilia treatment centers, and other providers.

In this document, Red Cross outlines our current purchasing and distribution system, and explains how this final rule's requirements will have a detrimental impact on ARC's products and ultimately the patients who need them. Sales and product data are included where appropriate to illustrate these explanations.

II. ARC Plasma Derivatives Products and Distribution

Sales and distribution of ARC derivative products occurs through arrangements involving ARC, a number of distributors, a firm which stores and manages the inventory of products, and with several Group Purchasing Organizations (GPOs).

All ARC derivative products are manufactured under contract arrangements with non-ARC fractionation firms. These firms also arrange for transportation from the manufacturing site

directly to one of the three warehouses owned and/or operated by the firm which manages storage and inventory on behalf of ARC under contract. This firm's functions include:

- Maintain products stored in a warehouse facility,
- Obtain customer orders for products including product type, number of units requested, and delivery dates,
- Prepare and package products for shipment,
- Arrange shipment scheduling, and
- Conduct customer invoicing.

ARC does *not* sell the product to the storage firm, nor does the storage firm charge either a commission or a mark-up fee. ARC pays the storage firm a service fee only. The storage firm does *not* advertise or market the products, nor do they maintain a sales staff or develop promotional materials on behalf of ARC. Although the storage firm will contact a shipment firm to arrange delivery, ARC negotiates the shipment contract, and pays the shipment firm for the delivery service. Therefore, it is ARC and their contract shipper who are responsible for product delivery.

Red Cross does not believe that the storage firm's functions meet the definition of "distribute" found on page 67756 in section 203.3(h): "Distribute means to sell, offer to sell, deliver, or offer to deliver a drug..."

FDA may have intended to include firms performing the inventory management function described above when describing distributors in section 203.3(dd): "Wholesale distributor means any person engaged in wholesale distribution of prescription drugs including.....**warehouses,** and wholesale drug **warehouses**..." (emphasis added)

By this wording, it is difficult to determine whether the term "warehouse" means ARC's storage firm, and the regulation provides no further definition of "warehouse" to aid clarification. However, the storage firm's functions are confined solely to those described above and do not include sales and delivery as required by section 203.3(h). Therefore, ARC believes that the storage firm could not be considered a "distributor" and that we must make arrangements with independent "distributors" to ensure our products reach the patients who depend on them.

III. Group Purchasing Organizations (GPO)

FDA appears to be granting some flexibility in meeting the rule's requirements by allowing hospitals and other entities to purchase from organizations that meet FDA's definition of GPO. As section 203.3(o) explains, a GPO "means any entity established, maintained, and operated for the purchase of prescription drugs for distribution exclusively to its membership..." Section 203.3(cc) indicates that:

> Wholesale distribution means distribution...to persons other than a consumer or patient, but does not include... The purchase or acquisition by a hospital or other health care entity that is a member of a group purchasing organization of a drug for its own use from the **group purchasing organization**... (emphasis added)

As Red Cross interprets these sections, a GPO may purchase products from a manufacturer. Hospitals, in turn, may purchase products from the GPO.

However, the GPOs Red Cross works with do *not* purchase products from ARC. Hospitals and other customers do *not* purchase products from GPOs. GPOs negotiate a product price on behalf of their members. In some cases, GPOs may help customers by selecting "authorized distributors" to handle product orders on behalf of their membership, but throughout the purchasing process, the GPO does *not* take ownership, or pay for, or sell, or deliver the product.

While well intended, these provisions will not aid Red Cross in its efforts to comply. Thus, distribution through GPOs is not a viable option for ensuring that patients receive ARC's products in the most expeditious manner possible.

IV. ARC Product Description

The Red Cross distributes three important products infused in the hospital outpatient setting: (1) antihemophilic factor (Monarc-M™), (2) two forms of immune globulin intravenous (IGIV), and (3) albumin. Red Cross also distributes PLAS✦® SD, a virally inactivated solvent/detergent treated human plasma product. As will be shown in the product descriptions below, Red Cross distributes a substantial amount of its plasma derivatives directly to customers and patients. ARC products sold over the last two fiscal years are contained in Table 1.

TABLE 1
UNITS OF ARC PRODUCTS[1]

Product	FY 1999 July 1, 1998 - June 30, 1999 (in Millions)	FY 2000 (to date) July 1, 1999 - May 31, 2000 (in Millions)
AHF-M (Monarch-M) (international units)	111.8	115.5
IGIV (Polygam® S/D) (grams)	2.0	2.1
IGIV (Panglobulin™) (grams)	1.4	0.8
Albumin (equivalent units)	1.7	2.4
PLASMA® SD (200 ml units)	0.2	0.3

Antihemophilic Factor

Antihemophilic Factor, which ARC sells under the trade name Monarc-M™ (Antihemophilic Factor (Human) Monoclonal Purified, Method M), is a vital infusible drug for persons with hemophilia A that may be administered daily, weekly, or monthly for control of or prophylaxis against bleeding. During FY 1999 (July 1, 1998 - June 30, 1999), ARC provided approximately 112 million international units of Monarc-M™. To date, sales have exceeded 115 million international units for FY 2000.

Monarc-M represent about 10% of the total market in the United States. There are approximately 13,320 cases of hemophilia-A[2] in the United States. ARC anticipates that its product is administered to approximately 1,300 patients each year. The distribution of Monarc-M™ is as follows:

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[1] Source: ARC internal product tracking report.

[2] Source: Souci, J. M.; Evatt, B.; Jackson, D. "Occurrence of Hemophilia in the United States." American Journal of Hematology, December 1998,-59(4):288-294. Note, there are approximately 3,640 cases of hemophilia B, but Monarc-M™ is used to treat hemophilia A patients only.

TABLE 2
Monarc-M™[3]
June 1, 1999 - May 31, 2000

Customer Description	Units (in Millions)	Percentage
Members of GPOs	18.4	16
Homecare Companies	12.3	11
State programs	1.7	2
Managed Care	4.9	4
Distributors	17.8	15
PHS Approved Facilities/Customers	35.2	30
International	15.8	14
Hospitals	12.7	11
Pharmacies	2.5	2
Blood Centers	1.0	1
Total	124.0	100

Clearly, the majority of this product, 85 percent, is provided directly to organizations that are not distributors including hospitals, home care companies, state programs, managed care companies, etc. Only 15 percent of the product involves distributors. Since the majority of this product is provided to customers who are not distributors, the regulation will have a highly significant impact on our ability to provide Monarc-M™ to patients suffering from hemophilia A. Thus, maintaining a viable distribution system for Monarc-M™, without disruption, is imperative for these patients.

IGIV

Immune globulins offer critical therapy to patients with a range of serious debilitating conditions such as immunodeficiency disease, B-cell chronic lymphocytic leukemia, and idiopathic thrombocytopenia. There are approximately 810,000 immune deficient patients who may benefit from IGIV treatment in the United States.[4] Red Cross distributes two forms of immune globulin, Polygam® S/D and Panglobulin™. Both products are human-derived and Polygam® S/D is solvent-detergent treated. Dosing of these products can occur up to three times per week.

[3] Source: ARC internal product tracking reports. Note: the time frame presented includes June of 1999 through May 2000 to provide a full year of data. Total units, therefore, will differ from those included in Table 1.

[4] Source: MRB Worldwide report; IDF Survey, 1998.

ARC's customers contact ARC's storage firm to place orders for IGIV products. ARC honors our obligations to our contract customers prior to filling orders from distributors who do not have contracts with us, usually with our remaining product. Data describing IGIV customers are included in the Table below.

TABLE 3[5]
IGIV
June 1, 1999 - May 31, 2000

	Polygam® S/D		Panglobulin™	
Customer Description	**Grams (In Millions)**	**Percent**	**Grams (In Millions)**	**Percent**
Distributors	2.1	89	0.7	86
Direct Purchase	0.2	10	0.1	14
International[6]	0.01	1	--	--
Total	2.3	100	0.8	100

Over the last year, ARC provided approximately 3 million total units of IGIV products, representing approximately 16 percent of the U.S. market share. Approximately 10 percent of the Polygam® S/D units and 14 percent of the Panglobulin™ units were sold to customers who were not distributors, an amount of product that would support slightly more than 12,800 infusion procedures.

IGIV is of especially great concern to ARC and to our patients, due to the critical shortages in recent years. Every unit is needed. Slowing or eliminating distribution of even a few grams could have serious impacts on the patient population. As shown above, failure to provide these products would impact thousands of treatments dependent on ARC's ability to provide products to patients who need them.

Albumin

The indications for albumin infusion include hypovolemia (with or without shock), hypoalbuminemia due to a variety of conditions such as malnutrition, burns, major injury, cirrhosis with ascites, nephrosis, and thyrotoxicosis. Thus, albumin patients are typically those suffering from burns, shock or other forms of trauma. A description of albumin customers is contained in the table below.

[5] Source: ARC internal product tracking reports. Note: the time frame presented includes June of 1999 through May 2000 to provide a full year of data. Total units, therefore, will differ from those in Table 1.

[6] ARC provided approximately 12,000 grams of Polygam® S/D.

TABLE 4[7]
ALBUMIN
JUNE 1, 1999 - MAY 31, 2000

Customer Description	Units (in millions)	Percent
Distributors	2.5	94
Direct Purchase	0.2	6
Total	2.6	100

Over the past year, ARC provided approximately 2.6 million units of albumin. As Table 4 demonstrates, approximately 94 percent of total albumin units are provided to distributors. The remainder were to direct contacts from United States customers (6 percent) who did not access a distributor. It should be noted that some of the customers who purchase direct include a large federal agency and a non-ARC blood center.

Although 6 percent of the direct purchasers appears to be a relatively small amount of the total units, this number is still highly relevant to our customers. For example, the amount of product provided directly to customers during this time frame could support approximately 13,000 to almost 56,000 infusion procedures. Clearly, enough procedures and patients are potentially impacted to be a public health concern if distribution of this product were disrupted.

PLAS+® SD

PLAS+® SD is a pooled, solvent/detergent viral inactivated human plasma product manufactured by V.I. Technologies and distributed by the American Red Cross. PLAS+® SD is manufactured from a pool of no more than 2,500 plasma donations. ARC supplies the volunteer donor plasma to V.I. Technologies. V.I. Technologies then prepares PLAS+® SD from ABO blood group specific units of frozen human plasma. The frozen plasma units are thawed, tested by polymerase chain reaction technology for parvovirus B19 DNA and if acceptable, pooled (combined) into lots containing no more than 2,500 donations. The thawed plasma is then solvent and detergent treated to inactivate lipid enveloped viruses, sterile filtered, tested again for parvovirus B19 DNA as well as hepatitis A RNA, and if acceptable, filled into blood bags at a standardized, 200 mL volume and refrozen. After packaging, the product is shipped to ARC's storage firm and placed in their warehouse.

[7] Source: ARC internal product tracking reports. Note: the time frame presented includes June of 1999 through May 2000 to provide a full year of data. Total units, therefore, will differ from those in Table 1.

PLAS✚® SD is indicated for the treatment of patients with documented deficiencies of coagulation factors for which there are no concentrate preparations available. These would include single factor deficiencies of factors I (fibrinogen), V, VII, X, XI, and XIII. Other indications for the use of this product include multiple coagulation factor deficiencies as might be seen in liver failure; reversal of warfarin effect; and, treatment of patients with thrombotic thrombocytopenic purpura (TTP), either chronic relapsing or acute. Typically, it is used like Fresh Frozen Plasma (FFP), i.e., it is transfused in the same manner, and for the same indications as FFP. FDA approved PLAS✚® SD for marketing on May 6, 1998. PLAS✚® SD was licensed as a "biologic" but is not listed with a national drug code, as are most derivatives.

The first full Fiscal Year of sales since licensure was FY 1999. Distribution increased from approximately 196,000 units in FY 1999 to approximately 239,000 units as of May 31, 2000, so that demand has increased during the second year of marketing.

ARC believes that PLAS✚®SD is excluded from the provisions of the PDMA. Section 203.3(y) indicates that the exclusion applies to blood and blood components "intended for transfusion," which clearly applies to PLAS✚® SD. Further, page 67722 of the preamble to the final regulation states that FFP and "plasma" are considered to be blood products, and therefore may be distributed directly by a blood center:

> "the agency has made a final determination that blood and blood components intended for transfusion should be excluded from all of the restrictions in and the requirements of PDMA...blood and blood components intended for transfusion include whole blood, red blood cells, plasma, fresh frozen plasma, cryoprecipitated AHF, and platelets..."

Thus, even though PLAS✚® SD is not specifically listed as being excluded from the rule's provisions, ARC believes that the use of PLAS✚® SD as "plasma", and specifically as an alternative to "fresh frozen plasma", should qualify this product as a blood component. Therefore the blood and blood component exclusion would apply to PLAS✚® SD.

However, ARC is commenting on PLAS✚® SD , because the definitions of blood and blood components contained in the regulatory text, and the manner in which PLAS✚® SD's license application was managed and issued by FDA, may lead the agency to a different conclusion.

The Center for Drug Evaluation and Research (CDER) reviewed ARC's original PLAS✚® SD license submission under a memorandum of understanding (MOU) agreed upon between the Center for Biologics Evaluation and Research (CBER) and CDER. CDER may believe that the MOU giving them oversight over the license review process implies that distribution of PLAS✚® SD should be managed in the same fashion as drugs.

Of greater concern is the rule's definition of "blood component". Section 203.3(d) states:

> Blood component means that part of a **single-donor** unit of blood separated by physical or mechanical means. (emphasis added)

Since PLAS✚® SD is formed by pooling donations of up to 2,500 donors, FDA may find that the definition of blood component pertaining to a single donor unit, does not allow the exclusion from the regulation for PLAS✚® SD.

Currently, ARC provides PLAS✚® SD by the following mechanisms:

- Direct requests from customers placed with the ARC storage firm,
- Direct requests by customers placed with ARC Regional blood centers, the primary means of distribution of this product.

As the table below demonstrates, this product is rarely provided through distributors.

TABLE 5[7]
PLAS✚® SD
July 1, 1999 - April 30, 2000

Customer Description	Units (in thousands)	Percent
Distributors	4.7	2
Direct Purchase	158.1	74
International	2.7	1
Non-ARC Blood Centers	48.3	23
Total	213.9	100

From July 1, 1999 through April 30, 2000, the most recent date for which ARC has complete distribution data, most requests for orders of PLAS✚® SD, about 98 percent, are made directly with ARC, usually ARC's Regional blood centers. One reason customers purchase this product from our regions is because they have established contracts for "blood components". A substantial amount, about 23 percent, is purchased

[7] Source: ARC internal tracking report. Note: total time frame for PLAS✚® SD differs from previous tables to reflect latest available data.

by non-ARC blood centers. Only about 2 percent of the product is provided to independent distributors.[8]

Thus, if FDA disagrees with our interpretation that PLAS✚® SD can be excluded under the blood and blood component provision, most of ARC's distribution system for PLAS✚® SD must be substantially restructured.

V. Overall Impact

The regulation's requirements would considerably weaken our ability to provide ARC products, including the likelihood of delays or outright failure to deliver the product to the patients. At a minimum, ARC must revamp the distribution systems described above for all derivative products, with special focus on ARC's antihemophilic factor product, Monarc-M ™. In other words, we must find a "middle man". The consequences are serious.

First is the potential for delay and/or the addition of several steps in the distribution process to attempt to avert delay in getting derivative products to the patients. To illustrate by a simple example, currently, a customer must only make one contact, i.e., directly to ARC's storage firm to place an order. If a customer must purchase through a distributor, the number of contacts may increase. The purchaser contacts a distributor, and, if the product is not directly available from the distributor, the distributor will contact ARC's storage firm.

Several other steps may be necessary, including:

- Amend existing contracts or establish new contracts with new distributors to expand the distribution capacity,
- Locate new or expand existing storage facilities,
- Amend or establish new transportation contracts to handle the alternative shipment arrangements including transport from ARC's storage facilities to a distributor's facility prior to reaching the ultimate customer.

Additional efforts are needed on the part of the hospitals and other organizations who currently purchase directly form ARC. They will need to negotiate agreements with distributors. Our customer's distributors must also have agreements with ARC. It is possible that in extreme cases, a customer may find that distributors maintaining

[8] Approximately 1 percent of ARC's PLAS✚® SD product is provided to International customers. ARC does not track the distribution patterns of the products provided to non-ARC blood centers or to International markets.

agreements with ARC are unable or unwilling to establish distribution arrangements with that customer. In those cases, the customer may need to find still another distributor with a working arrangement with an ARC distributor, which could result in two distributors involved between ARC and the ultimate customer.

While these steps are likely to slow day-to-day product delivery, they could become life threatening during a product shortage.

Complicating our ability to reestablish a distribution system, is the fact that the nature of the shortage may dictate the form that the distribution system should adopt, but neither the timing nor the characteristics of the shortage can be predicted.

The well-known IGIV shortage in 1998 was partially due to temporary reductions in industry production. However, future shortages could be due to different causes such as increasing demand for off-label usage or plant shut downs. Although more unusual disruptions, such as a transportation system labor strike, are unlikely, they cannot be ruled out as possibilities. Each cause of a shortage may require different planning or delivery arrangements. Since we cannot predict the cause of every potential shortage, it is inefficient, at best, to try to amend contracts and solicit distributors in anticipation of every possible contingency. At worst, it is infeasible.

Another major impact is the almost inevitable increase in product prices for the patients. Expenses will increase to cover the costs of such efforts as negotiating and managing distributor contracts, and for overseeing a less flexible purchase, storage, and distribution system. Expenses are also likely to increase to support the additional financial management and auditing procedures. Additional transportation and shipping expenses will occur if the distributor requires products to be shipped to their own storage facility prior to release to their customers. Moreover, there is the price "mark-up" added to ensure a profit margin for a distributor, who is unlikely to operate on a non-profit basis.

At the same time expenses are likely to increase, there will be a concurrent reduction in options for examining product distribution systems for cost savings opportunities as the market and transportation systems change over time. For example, if ARC finds efficiencies could be gained by building our own warehouse and distribution system staffed by ARC employees, we may be prevented from doing so.

Another serious concern is that some customers may not be able to obtain products at all. It may not be worth the effort for a distributor to negotiate a contract with smaller facilities with lower product demand or located in out-of-the-way rural areas.

The regulation is silent on its application to providing products to international patients. ARC provides products to governments and other entities in foreign countries that may not have the distribution systems we maintain in the United States. As a result, if a foreign country experiences a significant product shortage, ARC could be prevented

from assisting in a time of need. Further, international trade agreements should be evaluated to ensure that the PDMA rule is not in violation of them.

Finally, as PLAS+® SD illustrates, the distinction between blood components and plasma derivative products is blurred, and future generations of blood component products may take on more of the characteristics of derivative products. If the disadvantage of selling a plasma derivative in a restricted market environment remains, research on new technologies is likely to be restricted to the detriment of future product safety or production efficiencies.

In summary, if product shortages occur, they are likely to be exacerbated. Price increases are virtually inevitable and delays in getting the product to patients are very likely. Equally important, the regulation will not result in any public health improvement.

VI. Conclusion

The Red Cross requests that FDA revise the regulation to exclude organizations providing blood, blood components and plasma derivatives from the definition of "health care entity". This will allow these organizations to continue to provide life-saving products and ensure an adequate national supply of blood components, plasma derivatives and related products. The current exclusion of blood components from the provisions of PDMA highlights both Congressional and FDA concern about maintaining an adequate blood supply. Clearly, such concern is also warranted in the plasma derivative arena. Alternatively, the Red Cross urges FDA to expand the exclusion for blood and blood components to include plasma derivatives.

The American Red Cross appreciates this opportunity to express our concerns. If there are any questions, please contact Anita Ducca, Director, Regulatory Relations at 703-312-5601 (phone) by 703-312-5816 (fax), or by e-mail at DuccaA@USA.RedCross.org. Thank you.

American Red Cross

National Headquarters

February 4, 2000

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Re: Prescription Drug Marketing Act of 1987; Prescription Drug Amendments of 1992; Policies, Requirements, and Administrative Procedures - Final Rule (Docket Nos. 92N-0297 and 88N-0258, 64 Fed. Reg. 67720 (Dec. 3, 1999))

Dear Drs. Woodcock and Zoon:

The American Red Cross has reviewed the final rule on the procedures and requirements implementing the Prescription Drug Marketing Act (PDMA), as modified by the Prescription Drug Amendments of 1992 and the FDA Modernization Act of 1997. As the nation's single largest producer of blood-related products and a leading provider of blood-related services, the American Red Cross has a direct interest in the implementation of PDMA and its amendments.

After a careful review of the final rule's requirements, the American Red Cross wishes to share its concerns in the spirit of providing constructive feedback toward meeting the Agency's goal of ensuring the safest and most effective blood products, plasma derivatives, and related products and services.

The American Red Cross is concerned that the final rule does not exclude plasma derivatives from the procedures and requirements of PDMA. We believe this runs counter to the intent of Congress when it passed PDMA and FDA's own actions to exclude blood and blood components from PDMA's conditions. More importantly, failing to exclude plasma derivatives may hinder current and future efforts to improve distribution of such

life-saving products as Immune Globulin Intravenous (IGIV) and alpha-1 anti-tripsin at a time when the availability of these products has been tenuous at best.

We believe there is a very efficient way to address this concern. Specifically, we ask that the regulation be modified to exclude blood banks. In addition to the collection, processing, and distribution of blood products and components, blood banks are often responsible for the recovery of plasma from blood donors and/or the distribution of plasma derivatives. Excluding them from the definition of "health care entity" would keep in place the protections found within PDMA to ameliorate problems that the Act was intended to fix, i.e., to protect the public against the threat of subpotent, adulterated, counterfeit, and misbranded drugs posed by the existence of drug diversion schemes and drug diversion sub-markets. At the same time, excluding blood banks from the Final Rule's definition of "health care entity" would allow for the continued distribution of blood products and plasma derivatives in its current manner so as to ensure the most efficient distribution of these life-saving products. Alternatively, we suggest that FDA expand the exclusion for blood or blood components to include plasma derivatives.

Our assessment outlines the following areas:

- the role of the American Red Cross in the collection and distribution of blood components and plasma derivatives,
- the current exclusion of blood and blood components from the provisions of PDMA
- Congressional intent and statutory language arguing for the exclusion of blood banks from the definition of "health care entity", and
- supply concerns and reasons for excluding plasma derivatives and related products from the provisions of PDMA.

The American Red Cross would like to meet with FDA to discuss the issues presented in this letter, and possible avenues to change the final rule to the mutual benefit of FDA, the blood banking community, and the patients we serve.

We appreciate this opportunity to express our views. If you have any questions, please feel free to contact me at 703-807-5351 or Anita Ducca, Director, Regulatory Affairs at 703-312-5601.

Sincerely,

Jacquelyn Fredrick
Interim Senior Vice President
Biomedical Services

Attachment

cc: FDA Office of General Counsel
Joanne Binkley
Ann Wion
Robert Yetter
Steven F. Falter
Dockets Management Branch (HFA-305)
(Docket nos. 92N-0297 and 88N-0258)

American Red Cross

National Headquarters

American Red Cross Perspective
on the Policies, Requirements, and Administrative Procedures
of the Prescription Drug Marketing Act - Final Rule
(64 FR 67720; December 3, 1999)
Docket Nos. 92N-0297 and 88N-0258

I. THE AMERICAN RED CROSS

The American Red Cross (ARC/Red Cross) is an independent non-profit corporation. ARC is the largest supplier of blood products and one of the largest providers of blood services in the United States. Each year, the Red Cross collects, processes, and distributes approximately six million units of whole blood, representing half the nation's blood supply. Blood collection for transfusion is conducted throughout the nation by 36 regional Red Cross blood centers, utilizing several hundred registered auxiliary collection sites. The American Red Cross then processes these units of whole blood into specific components such as red blood cells, platelets, and other products that are distributed to thousands of hospitals and other health care providers.

The blood donated by Red Cross volunteers is also recovered and processed or fractionated into plasma derivatives. After collection and recovery, these plasma units are transported to several vendors with whom we have established contracts to manufacture antihemophilic factor, intravenous immune globulin, albumin and solvent-detergent treated products under the Food and Drug Administration (FDA/Agency) licenses of those companies. These plasma products are distributed under the American Red Cross label to hospitals, hemophilia treatment centers, and other providers. In all, Red Cross collects approximately 1.2 million liters of recovered plasma, accounting for about 10 percent of the nation's supply of plasma derivatives.

The American Red Cross also provides certain blood-related services to many hospitals throughout the United States.

II. EXCLUSION OF BLOOD AND BLOOD COMPONENTS

The final rule states that FDA has made a final determination "that blood and blood components intended for transfusion should be excluded from all of the restrictions in and the requirements of PDMA." These products include whole blood, red blood cells, plasma, fresh frozen plasma, cryoprecipitated AHF, and platelets. The Red Cross concurs with

FDA's determination and the rationale to exclude these products, as set forth in the September 1990 proposed rule on the Applicability to Blood and Blood Components Intended for Transfusion; Guidelines for State Licensing of Wholesale Prescription Drug Distributors (55 FR 38027). FDA also outlined its reasoning for this exclusion in the March 1994 proposed rule on Prescription Drugs, Policies, Requirements, and Administrative Procedures (59 FR 11842) - hereafter referred to as the "proposed rule". In that rule, FDA noted that blood and blood components should be excluded from the requirements of PDMA because

> "if PDMA were considered applicable to the distribution of blood and blood components, the result would be to impede the existing blood distribution system, thereby interfering with our nation's blood supply. Because application of PDMA to blood and blood components would produce this untenable result, FDA believes that Congress could not have intended to subject blood and blood components to PDMA's provisions."

We believe this reasoning is valid and appropriate. However, we point out that such reasoning also applies to plasma derivatives distributed by blood banks as evidenced by recent events surrounding shortages of some plasma derivatives, including some immune globulins and alpha-1 antitrypsin.

III. BLOOD BANKS AND THE DEFINITION OF HEALTH CARE ENTITY

PDMA generally prohibits the sale, purchase, or trade of a prescription drug that was purchased by a hospital or other health care entity, or donated or supplied to a charitable organization. It is our understanding that Congress enacted this law to preclude hospitals and other health care entities from obtaining pharmaceuticals at discounted prices and then reselling these drugs at a profit. According to the legislative history, this practice was considered to be unfair to wholesale and retail prescription drug distributors who had to pay average wholesale prices.

The final rule defines a health care entity as "any person that provided diagnostic, medical, surgical, or dental treatment, or chronic or rehabilitative care, but does not include any retail pharmacy or any wholesale distributor. A person cannot simultaneously be a health care entity and a retail pharmacy or wholesale distributor" (section 203.3(q)). However, section 503(c)(3) of the PDMA provides in part that:

> "For purposes of this paragraph, the term "entity" does not include a wholesale distributor of drugs or a retail pharmacy licensed under state law."

Red Cross interprets this statutory language as clear confirmation that PDMA explicitly allows for an exception to the Act's sales restrictions for wholesale drug distributors and retail pharmacies who are licensed under state law. As a result, we believe that the definition of "health care entity" in the final rule runs counter to the language in the PDMA since the definition in the final rule effectively precludes health care entities from obtaining state licensure to distribute drugs. Thus, the definition in the final rule is contrary to the intent of Congress by contradicting the clear and unambiguous language of Section 503(c)(3) of the PDMA.

FDA notes in its final rule that this line of reasoning runs counter to the Agency's interpretation of the above clause because allowing health care entities to obtain State wholesale distributor licenses could assist entities in circumventing the types of abuses that Congress sought to prevent through PDMA's provisions. Nevertheless, we suggest that language in the final rule relating to the definition of a health care entity runs counter to the Agency's own interpretation of section 503(c)(3) when it noted in the preamble to the proposed rule:

> "FDA interprets the first clause of the last sentence of section 503(c)(3) of the act to mean that the general prohibition against drug sales by hospitals, health care entities, and charitable institutions **was not intended to interfere with the operations of legitimate licensed prescription drug wholesalers and retail pharmacies."** (emphasis added)

Given that there has never been any indication of any distribution abuses of the type banned under PDMA with respect to any licensed blood products or plasma derivatives, it would appear that FDA's own interpretation of the clause prohibiting anyone from simultaneously being a health care entity and distributor would not apply to blood banks acting as legitimate licensed wholesalers. Neither prior to, or during, the extensive congressional investigations relating to PDMA were there any documented abuses that would suggest that Congress intended that blood centers be prohibited from simultaneously acting as health care entities and wholesale distributors. From the earliest implementation of PDMA, Representative John Dingell, then Chairman of the Subcommittee most directly responsible for the enactment of PDMA, sent a clear message that blood products should be exempted from the requirements and restrictions of PDMA. In a letter on September 29, 1988 to public docket No. 88N-0258 Mr. Dingell stated, in part:

> "The inclusion of blood and blood components in the Sales Restriction Section of the Act derives not from explicit language in the statute or legislative history, but rather by virtue of the fact that FDA had previously defined such products as 503(b) drugs by regulation [21 CFR 606.3(a) and (c)]."

It is important to note that FDA also defined plasma in this section at 21 CFR 606.3(d). Thus, reasons to exclude blood products and plasma derivatives from the prohibitions outlined in PDMA can be found through Congressional intent, FDA's own interpretative language in the proposed rule, and specific regulations already in place at the time PDMA was enacted.

In a letter to the FDA dated May 27, 1994, Congressman Dingell further noted that many full-service blood banks often serve as distributors of blood products and presumably comply with FDA regulations by registering with their respective states as wholesalers. He pointed out that FDA's proposed prohibition on a person simultaneously being a health care entity and a retail pharmacy or wholesale distributor suggested that such full-service blood banks that have registered with their respective states as a wholesaler would be prohibited from either providing blood components **or plasma derivatives** as part of their services (emphasis added). He noted that the Subcommittee understood that the FDA intended to address this issue in order to avoid disrupting the supply of biologics sold as prescription drugs to individuals such as hemophiliacs and individuals with compromised autoimmune systems.

The Red Cross believes that the FDA has not completely addressed this issue since the Agency has made no changes from the proposed rule to the final rule that would exclude blood banks from the restrictions outlined in the final rule or allow blood banks to serve as distributors of blood products and plasma derivatives.

IV. EXCLUSION OF PLASMA DERIVATIVES

Alternatively, if FDA determines that blood banks should not be excluded from the definition of "health care entity", the Agency should extend the exclusion from PDMA's sales restrictions for blood and blood components to include plasma derivatives and other related products. FDA has indicated in the final rule its view that the nation's supply of plasma derivatives would not be seriously impeded if blood banks were prohibited from distributing such products. However, as has been recently evidenced with several plasma

derivatives, the supply of such products can often be tenuous. Recent reports by the U.S. General Accounting Office, several Congressional hearings, and discussions at HHS and FDA advisory committee meetings have all highlighted intermittent supply problems affecting such products as Intravenous Immune Globulin and alpha-1 anti-trypsin.

Disrupting the distribution chain by prohibiting blood banks from distributing plasma derivatives would only exacerbate an already precarious situation. As noted previously, this is the very reason given by FDA to exclude blood and blood products from PDMA in order to avoid a situation that would:

> "seriously impede the present blood distribution system and thereby substantially interfere with, and reduce, the nation's blood supply. Based largely on this untenable result, the Agency stated its belief that Congress did not intend to subject blood and blood components to PDMA's provisions."

Furthermore, the legislative history shows no intent to cover blood or blood components intended for transfusion or plasma derivatives. Instead, Congress enacted PDMA to regulate the sales of prescription drugs distributed in traditional pharmaceutical marketing networks. Like blood and blood components, plasma derivatives are largely distributed outside this framework. In passing PDMA, Congress also sought to prevent the sale of out-dated and other unsafe and ineffective drugs through the "diversion" market. Due to the comprehensive system of FDA and HCFA regulations in place for blood banks, this is not a concern for blood and blood components intended for transfusion. Similarly, this regulatory system serves to protect the safety of plasma derivatives distributed through blood banks.

IV. CONCLUSION

The Red Cross requests that blood banks be excluded from the definition of "health care entity". This will allow blood banks to continue to provide life-saving products and ensure an adequate national supply of blood components, plasma derivatives and related products. The current exclusion of blood components from the provisions of PDMA highlight both Congressional and FDA concern about maintaining an adequate blood supply. Clearly, such concern is also warranted in the plasma derivative arena. Alternatively, the Red Cross urges FDA to exclude plasma derivatives from section 203.22(g).

The American Red Cross appreciates this opportunity to express our views on this regulation.